Remarks

The Office Action mailed August 12, 2003 has been received and reviewed. Claims 55, 58, 71, and 76 having been amended, the pending claims are claims 1-78. Claims 1-53 and 77-78 having been withdrawn from consideration, the claims currently under consideration are claims 54-76.

The specification has been amended at page 26, line 14, and page 47, line 22, to clarify that Applicants are not intending to recite a hyperlink therein. The specification has also been amended at page 41, lines 26-27 to correct obvious typographical errors, the correction of which is supported by the specification at, for example, page 42, lines 1-2. The specification has further been amended to add the label "SEQ ID NO:3" at page 42, line 7. The specification has been amended to correct typographical errors at page 45, line 24 and 25; page 46, line 10; page 47, line 15; page 48, line 15; and page 50, line 5, to correctly refer to Figure 1. Finally, the specification has been amended at page 49, line 19, and page 50, lines 13 and 14, to correct a typographical error to correctly recite the space group as $P3_221$, as would be obvious to one of skill in the art.

Claims 55, 58, and 76 have been amended to depend from claims 59, 66, and 74, respectively. Claims 55 and 58 have also been amended to recite the language "selected from the group consisting of." Claim 71 has been amended to recite "a" Baculovirus expression system.

Reconsideration and withdrawal of the rejections are respectfully requested.

Information Disclosure Statement

The Examiner acknowledged receiving Information Disclosure Statements filed as Paper Nos. 8 and 11, but apparently has been unable to locate the documents cited therein. As a courtesy, Applicants are attaching herewith copies of the 1449 forms (EXHIBIT A, 7 pages) and documents listed therein, which were filed with Information Disclosure Statements on March 1, 2002 and September 9, 2002. Consideration of each of the documents listed on the

attached 1449 form(s) is respectfully requested. Pursuant to the provisions of M.P.E.P. §609, Applicants further request that a copy of the 1449 form(s), marked as being considered and initialed by the Examiner, be returned with the next Official Communication.

Copending Application

Applicants directed the Examiner's attention to copending application Serial No. 10/027,277 in the Information Disclosure Statement mailed March 1, 2002. Applicants also wish to draw the Examiner's attention to the Office Action mailed September 8, 2003, and the rejections recited therein, for copending application Serial No. 10/027,277.

Restriction/Election of Species Requirement

Applicants thank the Examiner for reconsidering the Restriction Requirement mailed May 12, 2003, and rejoining Group VIII (claims 54-71) with elected Group IX (claims 72-76). Applicants also thank the Examiner for reconsidering and withdrawing the Election of Species Requirement for Group VIII.

Sequence Listing

The Examiner alleged that the present application fails to comply with the requirements of 37 C.F.R. §1.821 through 1.825. Specifically, the Examiner pointed to page 42, line 7. Applicants respectfully disagree.

Applicants note that the synthetic peptide listed at page 42, lines 6-7 is identical to the synthetic peptide identified elsewhere in the specification as SEQ ID NO:3 (e.g., page 12, lines 2-3, as amended; page 45, lines 8-9, as amended). However, in the interest of expediting the prosecution of the present application, the specification has been amended herein at page 42, line 7, to identify the sequence of the synthetic peptide as SEQ ID NO:3.

Applicants respectfully submit that the present application is in compliance with the requirements of 37 C.F.R. §1.821 through 1.825.

Provisional Statutory-Type Double Patenting Rejection

Claims 54-76 were provisionally rejected under 35 U.S.C. §101 as claiming the same invention as that of claims 1-23 of copending Application Serial No. 10/027,277. Claims 54, 56, and 72-76 were provisionally rejected under 35 U.S.C. §101 as claiming the same invention as that of claims 4, 5, and 24-28 of copending Application Serial No. 10/144,441.

Upon an indication of otherwise allowable subject matter and in the event this rejection is maintained, Applicants will provide an appropriate response.

Provisional Obviousness-Type Double Patenting Rejection

Claims 54, 55, and 57-71 were provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-3 and 6-23 of copending Application Serial No. 10/144,441.

Upon an indication of otherwise allowable subject matter and in the event this rejection is maintained, Applicants will provide an appropriate response.

Objections to the Specification

The Examiner objected to the specification for allegedly containing an embedded hyperlink. The specification having been amended at page 26, line 14, and page 47, line 22, Applicants respectfully submit that the objection has been rendered moot.

The Examiner also objected to the specification for referring to Figure 1B. The specification having been amended at page 45, lines 24 and 25; page 46, line 10; page 47, line 15; page 48, line 15; and page 50, line 5, Applicants respectfully submit that the objection has been rendered moot.

Finally, the Examiner objected to the specification for referring to an invalid space group. The specification having been amended at page 49, line 19; and page 50, lines 13 and 14, Applicants respectfully submit that the objection has been rendered moot.

In view of the amendments and remarks presented herein above, Applicants

respectfully request that the Examiner reconsider and withdraw the objections to the specification.

Objections to the Claims

The Examiner objected to claims 55 and 58 for allegedly using an improper alternative limitation "selected from the group of." Applicants disagree, and respectfully submit that the claim language "selected from the group of" clearly and distinctly conveys the claimed invention to one of skill in the art. However, in the interest of expediting the prosecution of the present application, claims 55 and 58 have been amended to recite "selected from the group consisting of," and the objection is rendered moot. Applicants respectfully request that the Examiner reconsider and withdraw the objection to the claims.

Rejection under 35 U.S.C. §112, Second Paragraph

The Examiner rejected claims 55, 58, 71, and 76 under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention.

Specifically, the Examiner rejected claims 55, 58, and 71 for allegedly having insufficient antecedent basis. Claims 55, 58, and 71 having been amended, Applicants respectfully submit that the rejection has been rendered moot.

The Examiner rejected claim 76 for lack of clarity. Claim 76 having been amended to depend from claim 74, Applicants respectfully submit that the rejection has been rendered moot.

Based on the amendments and remarks presented herein above, reconsideration and withdrawal of the rejections under 35 U.S.C. §112, second paragraph, is respectfully requested.

Rejection under 35 U.S.C. §112, First Paragraph

Written Description

The Examiner rejected claims 54-76 under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Specifically, while acknowledging that the present specification discloses a "representative species of the genus of purified human beta secretases, inhibitors thereof, or crystals of beta secretases from any source," he asserted that "[t]he specification fails to describe any additional representative species of the claimed genera of purified human beta secretases, inhibitors thereof, or crystals of beta secretases from any source" (page 7, lines 18-24 of the Office Action mailed August 12, 2003). Applicants respectfully traverse the rejection.

"To satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention." M.P.E.P. §2163. Factors to be considered in determining whether there is sufficient evidence of possession include the level of skill and knowledge in the art, partial structure, physical and/or chemical properties, functional characteristics alone or coupled with a known or disclosed correlation between structure and function, and the method of making the claimed invention.

Applicants respectfully submit that the specification (including, for example, the originally filed claims) provides an adequate written description for a method for crystallizing a human beta secretase molecule or molecular complex (e.g., claims 54-71). Method claims 54-71 recite appropriate crystallization conditions including, for example, pH (e.g., independent claim 54 and dependent claim 56), method for isolation of the human beta secretase (e.g., claims 68-71), concentration of the human beta secretase (e.g., claim 64), concentration of inhibitor (e.g., claim 65), the presence of salts (e.g., claim 55, as amended, and claims 59-60), the presence of buffers (e.g., claim 57), and the presence of glycols, glycerols, or solvents (e.g., claim 58, as

amended, and claims 61-63 and 66-67). Thus, Applicants respectfully submit that the specification adequately supports a method for crystallizing a human beta secretase molecule or molecular complex (e.g., claims 54-71).

Further, Applicants respectfully submit that the specification (including, for example, the originally filed claims) provides an adequate written description for crystals of beta secretase (e.g., claims 72-76). Crystal claims (e.g., claims 72-76) recite various parameters including, for example, space group symmetry (e.g., independent claims 72 and 74), unit cell dimensions (e.g., independent claims 73-74), and amino acid sequences (e.g., claims 75 and 76). Thus, Applicants respectfully submit that the specification adequately supports crystals of beta secretase (e.g., claims 54-76).

Moreover, in Trilateral Project WM4 on *Comparative study on "protein 3-dimensional (3-D) structure related claims*, in referring to a hypothetical claim (i.e., "A crystalline form of protein P having unit cell dimensions of a=4.0nm, b=7.8nm, and c=11.0nm") stated that "[t]he claim complies with the written description requirement because the structure of protein P is provided." Trilateral Project WM4 on *Comparative study on "protein 3-dimensional (3-D) structure related claims*, Annex 3, Case 4, A3 (http://www.uspto.gov/web/tws/wm4/pdf/wm4_3d_annex_3.pdf). Applicants respectfully submit that the present specification provides the structure of beta secretase. *See, for example*, the atomic structure coordinates listed in Tables 1 and 3, and described, for example, at page 12, line 24 to page 13, line 8 of the specification.

Based on the remarks presented herein above, Applicants respectfully submit that the specification recites structural, physical, and chemical properties, along with a method of making the claimed invention, sufficient to satisfy the written description requirement under 35 U.S.C. §112, first paragraph.

Enablement

The Examiner rejected claims 54-76 under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Specifically, the Examiner acknowledged that the specification is "enabling for a method for crystallizing the human beta secretase of SEQ ID NO:1 complexed with the human beta secretase inhibitor of Figure 1," but asserted that the specification "does not reasonably provide enablement for a method for crystallizing *any* human beta secretase molecule or molecular complex by preparing purified human beta secretase in the presence of *any* inhibitor and crystallizing human beta secretase from *any* solution having a pH of about 3.5-5.5" (page 9, lines 1-12 of the Office Action mailed August 12, 2003). Applicants respectfully traverse the rejection.

"A specification disclosure which contains a teaching of the manner and process of making and using an invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as being in compliance with the enablement requirement of 35 U.S.C. 112, first paragraph, unless there is a reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support." M.P.E.P. §2164.04. "As long as the specification discloses at least one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim, then the enablement requirement of 35 U.S.C. 112 is satisfied." M.P.E.P. §2164.01(b). "For a claimed genus, representative examples together with a statement applicable to the genus as a whole will ordinarily be sufficient if one skilled in the art (in view of level of skill, state of the art and the information in the specification) would expect the claimed genus could be *used* in that manner without undue experimentation. Proof of enablement will be required for other members of the claimed genus only where adequate reasons are advanced by the examiner to establish that a person skilled in the art could not *use* the genus as a whole without undue experimentation." M.P.E.P. §2164.02, paragraph entitled "WORKING

EXAMPLES AND A CLAIMED GENUS" (emphasis added). "[E]ven in unpredictable arts, a disclosure of every operable species is not required." M.P.E.P. §2164.03.

Applicants respectfully submit that, as described herein above, the specification adequately describes a method for crystallizing human beta secretase. Further, although not required, the specification includes working examples of a method for crystallizing human beta secretase (e.g., page 45, line 22 to page 47, line 5). The specification also provides methods of using the claimed crystals (e.g., homology modeling and rational drug design, page 31, line 21 to page 39, line 12). Moreover, the Examiner has not provided any reason to doubt the objective truth of the disclosure provided in the specification.

However, the Examiner alleged that a "high degree of unpredictability in the art is supported by the state of the art" (page 11, line 9 of the Office Action mailed August 12, 2003). The Examiner supported his argument by noting disclosures of different human beta secretase crystals. Specifically, the Examiner noted that the crystal of Chopra et al. was crystallized at pH 6.5; the crystal of Tang et al. at pH 6.4; and the crystal of Hong et al. at pH 7.4 (paragraph spanning pages 11-12 of the Office Action mailed August 12, 2003). Notably, each human beta secretase crystal noted by the Examiner to support unpredictability was crystallized at a pH outside the presently claimed range, i.e., a pH of about 3.5 to about 5.5 (e.g., independent claim 54). Thus, Applicants respectfully submit that one of skill in the art could prepare human beta secretase crystals using the method as claimed (e.g., claims 54-71) without undue experimentation.

The Examiner also asserted that "replacement of methionine with selenomethionine in a given protein alters the amino acid and chemical composition of the protein. Thus, when crystallized, such homologs, splice variants, and selenomethionine mutants may pack differently forming different crystals from that of the protein of SEQ ID NO:1, even under identical crystallization conditions (page 12, lines 17-20 of the Office Action mailed August 12, 2003). Applicants respectfully note that method claims 54-71 do not recite packing properties of the crystals formed. Thus, Applicants respectfully submit that the Examiner's

arguments are not commensurate in scope with the claims. Further, one of skill in the art would not necessarily expect replacement of a methionine with selenomethionine to result in different packing properties. Replacement of methionine by selenomethionine is well known in the art of protein crystallography as a method of incorporating heavy atoms into a molecule to aid in the solution of the x-ray crystal structure for the native molecule (e.g., without selenomethionine). The technique is useful *specifically* because the incorporation of the heavy atoms does not substantially disrupt the crystal structure. *See, for example*, Hendrickson et al., "Selenomethionyl proteins produced for analysis by multiwavelength anomalous diffraction (MAD): a vehicle for direct determination of three-dimensional structure," *EMBO J.*, 9:1665-1672 (1990) (listed on a 1449 form submitted March 1, 2002, with an Information Disclosure Statement, and included in the courtesy copies of replacement documents submitted herewith).

Moreover, Applicants respectfully submit that one of skill in the art, using the disclosure provided in the specification (including the working examples), would be able to make and use the entire scope of the invention as recited in claims 54-76. For example, Applicants' Representatives respectfully submit that the present disclosure of methods of making and using crystals of human beta secretase provides enablement for one of skill in the art, without undue experimentation, to make additional crystals of human beta secretase. For example, Applicants' Representatives respectfully submit that the presently disclosed crystals provide enablement for one of skill in the art to use the crystals in, for example, cross-seeding techniques (*see* the specification at, for example, page 46, lines 4-21, for disclosure of seeding) to make additional crystals of human beta secretase. Thus, Applicants respectfully submit that claims 54-76 are fully enabled by the specification.

Based on the remarks presented herein above, Applicants respectfully request that the Examiner reconsider and withdraw the rejections under 35 U.S.C. §112, first paragraph.

Summary

It is respectfully submitted that all the pending claims are in condition for allowance and notification to that effect is respectfully requested. The Examiner is invited to contact Applicants' Representatives, at the below-listed telephone number, if it is believed that prosecution of this application may be assisted thereby.

Respectfully submitted for
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CERTIFICATE UNDER 37 CFR §1.10:
"Express Mail" mailing label number: **EV 073687877 US** Date of Deposit: **FEBRUARY 12, 2004**
The undersigned hereby certifies that the Transmittal Letter and the paper(s) and/or fee(s), as described hereinabove, are being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR §1.10 on the date indicated above and is addressed to the Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

By: _____
Name: SAM HER